Acute lymphoblastic leukemia in infants

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Between January 1978 and August 1999, 29 infants with newly diagnosed acute lymphoblastic leukemia (ALL) were treated on three consecutive protocols. Eighteen patients with infant ALL diagnosed between 1978-1991 were included in Group 1. In this group, treatment comprised a two-or three-drug induction with prednisolone, vincristine and L-asparaginase, and maintenance therapy consisted of weekly oral administration of mercaptopurine and methotrexate for three years. Group 2: Between 1991 and 1999, 11 infants with ALL were treated by St. Jude Total Therapy XI (n=4) and XIII (n=7) protocols with minor modification. Three years' event-free survival (±SE) was 14±9% in group 1. In group 2, this rate was 25±22% in Total XI and 57±19% in Total XIII. Outcome for infants on protocols Total Therapy XI and XIII improved compared with that of group 1.

Key words: infant leukemia, acute lymphoblastic leukemia, high-dose methylprednisolone.

Acute lymphoblastic leukemia (ALL) in infants, which usually occurs within the first 12 months of life, is different from that seen in other age groups. It is usually characterized by the presence of high leukocyte counts at diagnosis, massive organomegaly, central nervous system involvement, the absence of CD10 expression, the coexistence of myeloid-associated antigens, high frequency of mixed lineage leukemia (MLL) and extremely poor prognosis[1-4]. Both acute and long-term complications of treatment for infant acute lymphoblastic leukemia are also frequent[3,5,6]. It has been reported that infant ALL accounts for 2.5 to 5% of pediatric cases[7]. Several studies have shown that infant ALL has poor prognosis. However, the number of survivors has increased with the recent treatment protocols[3,5,6].

We here report the results of modified St. Jude Total Therapy Studies XI and XIII and compare them with previous treatment protocols.

Material and Methods

Between January 1978 and August 1999, 1,318 children were diagnosed as having ALL. Twenty-nine (2.2%) of them were below 12 months of age. The patients were retrospectively analyzed at Hacettepe University, Department of Pediatrics, Section of Pediatric Hematology. The patients were divided into two groups according to treatment schedule.

Eighteen patients with infant ALL diagnosed between January 1978 and February 1991 were included in Group 1. Treatment comprised a two-or three-drug induction with prednisolone, vincristine, and L-asparaginase. Central nervous system prophylaxis was given to three patients.

Maintenance therapy consisted of weekly oral administration of 6-mercaptopurine and methotrexate for three years[8,9]. Cytogenetic analysis and immunophenotyping studies could not been performed in Group 1.

Group 2: Between March 1991 and August 1999, 11 infants with ALL were treated by the previously described modified St. Jude Total Therapy Studies XI (n=4) and XIII (n=7) with minor modification including high-dose methylprednisolone (Table I)[10-12]. In March 1997, the Total XI study was changed to Total XIII protocol, which is more intensive. Central nervous system (CNS) directed therapy comprised a course of five intrathecal injections. Cranial radiation 18 Gy was given to three patients. Cranial radiation was deferred until after the second year of life. Cytogenetic analysis by banded metaphase analysis was performed in five patients in the second group.

Table I. Treatment Schema of Modified Total Studies XI and XIII

	Study XI		Study XIII	
	Group A	Group B	Higher risk	Lower risk
Induction	P.VDA→E+Cy+C	HDMP.VDA→ECyC	HDMP.VDA→E+C	HDMP.VDA→E+C
Consolidation	HDMTX	Same	HDMTX+MP	HDMTX+MP+HDMTX+MP
Continuation				
	E+Cy	Same	E+Cy	MP+MTX
	MP+MTX		MP+MTX	MP+MTX
	E+C		MTX+C	MP+MTX
	P+V		P+V+Aa	P+V
	Rotated weekly		E+Cy	MP+MTX
			MP+HDMTXb	MP+MTX
			E+C	MP+HDMTXb
			P+V+A	P+V
			Rotated weekly	
Reinduction	No	No	PVDA	No
			E+C	
			HDMTX	
			From weeks 32 to 37	
CNS Therapy	TIT+CRT	TIT+CRT	TIT+CRT	TIT

P: prednisone; HDMP: high-dose methylprednisolone; V: vincristine; D. daunorubicin; A: asparaginase; C. cytarabine; E: etoposide; HDMTX: high-dose methotrexate; MP: mercaptopurine; Cy: cyclophosphamide; MTX: methotrexate; TIT: triple intrathechal therapy with methotrexate, prednisolone and cytarabine; CRT: cranial irradiation for patients with high-risk leukemia or CNS leukemia at diagnosis.

[a]Asparaginase discontinued after week 28 of continuation therapy.
[b]High-dose methotrexate discontinued after one year of continuation therapy.

The leukemia was considered to have a T-cell origin if the blast cells expressed at least two of the antigens CD7, CD5, CD3, CD2; to be precursor B cell leukemia if the blast cell expressed at least two of the antigens CD19, CD20, CD22; and to be CALLA positive cell if the blast cells expressed the antigen CD10.

Event-free survival (EFS) was estimated by Kaplan Meier analysis of data updated as of July 2002. EFS was calculated from the first day of treatment to the time of analysis or to the first event (early death, resistance, relapse, death during complete remission or secondary malignancy).

Results

The clinical and some laboratory data at diagnosis are shown in Table II. Age, gender, and some risk factors were similar in the two groups. Response to therapy and outcome are also summarized in Table II. Cytogenetic analysis showed normal karyotype in all five patients of Group 2.

Group 1: Two patients had early deaths, five patients did not accept treatment and three infants failed to achieve remission. Eight patients achieved complete remission. One patient died of sepsis in remission. A total of seven relapses occurred in eight patients in bone marrow (BM) (n:3), CNS (n:2) and combined (BM+CNS, BM+ testes) (n:2), respectively. Two of them had relapse at the 63rd (BM+testes) and 60th month (BM+CNS) of therapy; however, they are still long-term survivors at 15 and 24 years. They were treated with intensive chemotherapy following relapse.

Group 2: All patients in Group 2 achieved a complete remission at the end of induction. Four of 11 patients (27%) in Group 2 died at 1, 1.5, 2 and 30 months of therapy from sepsis (2 patients), metabolic problems (1 patient) and pneumococcal meningitis (1 patient), respectively. Two patients (18%) had BM relapse at the 9th and 5th month of therapy. No remission at 15th day of induction was obtained in either of them. One patient had bone marrow transplantation from compatible sibling donor in first remission; EFS however, it resulted in rejection. She is in remission 20 months after rejection. The EFS rate (±SE) was 45±15% at three years in Group 2. In Total Study XI (n=4) and XIII (n=7), EFS rates were 25±22% and 57±19% at three years, respectively. Figure 1 shows EFS for children in the two groups.

Immunophenotyping was performed in 10 patients in Group 2. No reactivity to the tested antibodies was observed in one infant. Four infants had CD10-positive B-lineage. Five patients had CD10-negative B-lineage. Three of

Table II. Some Data of the Patients in Both Groups

	Group 1		Group 2	
	n=18	%	n=11	%
Median age (mo)	6 (1-12)		9 (5-12)	
<6 mo	7	41	2	18
≥6 mo	11	59	9	82
Gender (M/F)	9/9		6/5	
Hemoglobin (g/dl)	8.6 (3.3-10)		9.2 (4.7-11.2)	
WBC (10^9/L)				
<50	9	50	6	55
≥50	9	50	5	45
Mediastinal lymphadenopathy at diagnosis	1	5.5	2	18
CNS involvement at diagnosis	2	11	–	–
Hepatosplenomegaly >5 cm	10	55	8	72
Early death	2		–	–
Did not accept treatment	5		–	–
Complete remission	8	72	11	100
No remission	3	28	–	–
Relapse				
Bone marrow	4		2	
CNS	2	–		
Combined	1	–		
Deceased at remission	1	9	4	36
Survival rate	2*	11	5	45

* Long-term survival after relapse.

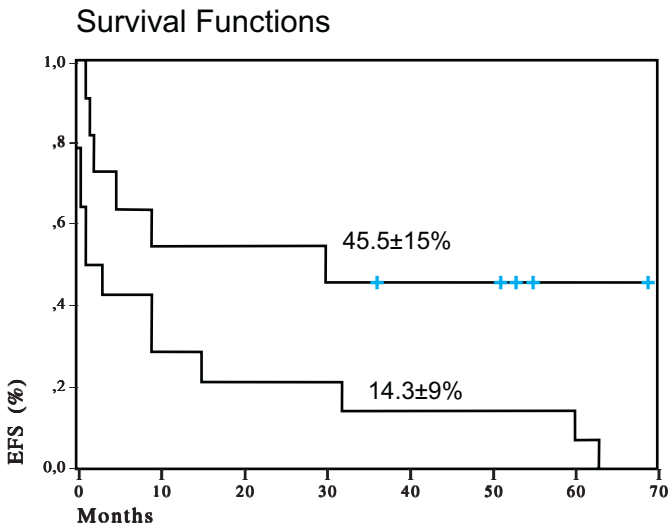

Fig. 1. Event-free survival (EFS) rate in Group 1 and Group 2 patients.

five infants with negative CD10 expression are alive. Seven patients had L1 type, and four of them (57%) are alive. L2 type was present in four children, only one of them (25%) is alive. Some data regarding Group 2 infants is shown in Table III.

Discussion

Recent studies have shown that the number of survivors has increased with use of the intensive treatment protocols[5,6,13]. The present study revealed that the outcome of infant ALL treated with intensive multiagent chemotherapy

Table III. Analysis of 11 Patients in Group 2

	Number	%	Alive	%	Deceased	
FAB morphology						
L1	7	63	4	57	3	43
L2	4	37	1	25	3	75
Immunophenotype						
CALLA-B cell	5	45	1	20	4	80
CALLA+B cell	4	37	3	75	1	25
Null	1	9	–	–	1	100
Undetermined	1	9	1	100	–	
Family cancer history	1	9	1	100	–	–
Use of maternal drug	2	18	2	100	–	–
Treatment						
Total XI	4	37	1	25	3	75
Total XIII	7	63	4	57	3	43

is better than that experienced with the previous treatment schedule. The presence of late relapses and administration of intensive chemotherapy after relapse in two infants with leukemia may be responsible for long-term survival in Group 1 with only one infant dying of sepsis in remission. Three infants in Group 1 failed to achieve remission.

In Group 2, EFS rate was 45% at three years (in Total Study XI 25%, in Total Study XIII 57%). Recently, similar results have been reported by St. Jude Children's Research Hospital (n=11, 36.4% and n=5, 20% at 10 years in Total Study XI and XIII, respectively)[11] and by the Berlin-Frankfurt-Münster group (Trial ALL-BFM 86) (n=33, 36% at 6 years)[14]. In contrast to the St. Jude group, we found higher EFS in Total XIII than Total XI. This result may be explained by the small number of patients and follow-up time.

No cytogenetic abnormality was detected in our patients. This could be due to either our technical limitations or to the limited number of our patients.

Remission was achieved in all patients in Group 2, and the mortality rate was 55%. Two patients (33%) died of relapse and four infants (67%) died in remission. Two patients with relapse had lack of CD10 expression and they did not have remission in bone marrow by day 15. This data indicates that lack of CD10 expression is a poor prognostic factor and that early response to treatment is a good prognostic factor, as previously reported[1,2,6]. The remission rate is high via intensive chemotherapy protocols including St. Jude XI and XIII, but there is an increased risk of death from complications including infection and metabolic events in remission. The physiologic hypogammaglobulinemia of infancy associated with myelosuppression may also be responsible for sepsis in this period.

Infants with ALL treated on St. Jude protocols XI and XIII in the present study had a superior outcome to those treated with the prior treatment schedule in Group 1. Previously survival improved for patients with acute lymphoblastic leukemia by using high-dose methylprednisolone (HDMP)[9]. The addition to HDMP instead of standard dose steroids to conventional antileukemic regime in the present study might have improved the prognosis of infant ALL in the second group as has been previously reported in children with ALL[11,12].

The incidence of bone marrow and CNS relapses was lower in Group 2 than in Group 1. This data indicates that high-dose methotrexate and HDMP and intensification may prevent marrow and CNS relapses.

In conclusion, although intensification of chemotherapy could improve poor prognosis of ALL in infants, three-year EFS is still disappointing and the current therapy is inadequate. Excessive toxicities and treatment-related deaths were present in infants treated by intensive chemotherapy despite encouraging overall results.

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